Response

Diabetes Metab J 2019;43:729-730
https://doi.org/10.4093/dmj.2019.0178
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Increased Serum Angiopoietin-Like 6 Ahead of Metabolic Syndrome in a Prospective Cohort Study (*Diabetes Metab J* 2019;43:521-9)

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We really appreciate Dr. Kim for expressing interest and providing valuable comments on our recently published article, "Increased serum angiopoietin-like 6 ahead of metabolic syndrome in a prospective cohort study" which was published in *Diabetes & Metabolism Journal* [1].

Positive energy balance, increased adiposity, and inflammation are the major pathogenic components of metabolic syndrome [2]. Along with these metabolic stresses, anthropometric values and serum biomarker levels reflecting metabolic status alter, which can be used as predictors for metabolic syndrome [3,4]. These alterations are likely consequences of disease progression and participate in vicious cycles leading to aggravation of metabolic syndrome. However, a substantial portion of hepatokines, myokines, and adipokines shows increased expressions upon metabolic insult to attenuate disease progression. Their roles are concluded as a resilience against metabolic stress, which is opposite to conventional biomarkers. Angiopoietin-like 6 (ANGPTL6) is one example, since animal studies have demonstrated its beneficial influences on body metabolism including augmentation of energy expenditure and improvement of insulin sensitivity [5]. These actions of ANGPTL6 are required to relieve the burden of metabolic stress, and expression and secretion of ANGPTL6 might be induced by pathogenic components of metabolic disease. Therefore, an elevated ANGPTL6 level indicates the existence of metabolic stress requiring compensatory actions. Previously, we confirmed in mouse models that serum ANGPTL6 levels were increased by high fat diet and attenuated by exercise training [6]. Based on this, we interpreted our results in a prospective cohort study that upregulation of ANGPTL6 is a protective response alleviating metabolic stress [1]. We suggest that increased serum ANGPTL6 levels in a preclinical status reflect the increase in ongoing metabolic stress; thus, it could be used as a predictable biomarker of development of metabolic syndrome.

As the first prospective study, we provided evidence of a chronological relationship in which increased serum ANGPTL6 level precedes the onset of metabolic syndrome. As suggested by Dr. Kim, this study needs to be expanded to monitor ANGPTL6 levels during a follow-up period. We speculate the continuance of high ANGPTL6 level during the progression of metabolic syndrome and ANGPTL6 may work as a prognostic biomarker. This anticipation is also based on our previous observation in a cross-sectional study that showed a significantly increased serum level of ANGPTL6 in metabolic syndrome patients [7]. Nevertheless, we could not exclude the possibility that the increased ANGPTL6 level might be diminished at the late stage of metabolic deterioration. Hence, we are planning to compare the changes in ANGPTL6 according to disease severities as the progression of metabolic syndrome in the follow-up

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period. We definitely agree with Dr. Kim's suggestion to enlarge the cohort population size and to apply a risk-scoring system. In addition, further study is required to identify the mechanisms of ANGPTL6 upregulation including a sensing mechanism of metabolic stress and upstream signals of ANGPTL6. Previously, we had introduced leptin as an upstream regulator of ANGPTL6 [6], but more extensive identification of regulatory mechanisms for ANGPTL6 expression is needed. Finally, high ANGPTL6 level in metabolic syndrome patients can be interpreted as ANGPTL6 resistance, because increased ANGPTL6 failed to compensate for metabolic stress. To elucidate ANGPTL6 resistance, identification of ANGPTL6, which is still unknown, and its alteration in expression and signaling pathway upon metabolic stress are necessary in further study.

We thank Dr. Kim again for the thoughtful comments and welcome any further discussion.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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